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Results of kidney transplantation from suboptimal donors to recipients of the older age group

B.Z. Khubutiya✉[1], M.Sh. Khubutiya[1,2], A.K. Evseev[1], A.V. Babkina[1,2]

[1]*N.V. Sklifosovsky Research Institute for Emergency Medicine, 3 Bolshaya Sukharevskaya Sq., Moscow 129090 Russia;*

[2]*Department of Transplantology and Artificial Organs, A.I. Yevdokimov Moscow State University of Medicine and Dentistry, 20 Bldg. 1 Delegatskaya St., Moscow 127473 Russia*

✉Corresponding author: Bidzina Z. Khubutiya, Physician of the Kidney and Pancreas Transplantation Department of N.V. Sklifosovsky Research Institute for Emergency Medicine, HubutiyaBZ@sklif.mos.ru

Abstract

Introduction. *Among the growing number of patients with chronic renal failure who need dialysis therapy or kidney transplantation, a significant proportion are people over 60 years old, making from 30 to 45% of all patients who need dialysis, according to various sources. The elderly age of the recipient contributes to the risk of developing graft dysfunction due to the presence of concomitant diseases that worsen the immediate and long-term results of transplantation. And the probability of receiving a kidney graft in elderly patients is significantly lower than in young recipients. One of the ways to solve this problem is to use kidneys from suboptimal donors.*

Material and methods. *The analysis of clinical examinations, laboratory and instrumental test results obtained in 124 patients who underwent cadaveric kidney allotransplantation at the N.V. Sklifosovsky Research*

Institute for Emergency Medicine, including that from suboptimal donors, was carried out. Of these, 69 (55.6%) recipients aged 60 years and older were included in the main group (group 1), and 55 recipients younger than 60 years (44.4%) in the comparison group (group 2).

Results. *Kidney transplantation to elderly patients (aged 60 years and older), including from a suboptimal donor, provides a sufficiently high efficiency with a 1-year recipient survival rate of 98.6% and a functioning graft for 1 year in 75.4% of cases, which does not differ from the survival rate of younger recipients (98.2%), but is inferior by the case rate of keeping the graft functioning (91.9%). Meanwhile, the parameters characterizing the functional state of the transplanted organs that maintained their function for 1 year did not differ statistically significantly between elderly and younger recipients.*

Conclusions. *The results of the study showed that kidney transplantation from suboptimal donors to patients of the older age group provides acceptable results with low mortality of recipients and a 1-year functioning of the graft in 75% of cases. This makes it possible to increase the availability of kidney transplantation for patients of the older age group and achieve better survival results, provided adequate selection of recipients and an objective assessment of the quality of transplanted organs.*

Keywords: kidney transplantation, suboptimal donors, patients of the older age group, elderly recipients, survival

CONFLICT OF INTERESTS Authors declare no conflict of interest

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ESRD, end-stage renal disease
RR, relative risk

Introduction

In most countries where kidney transplantation is performed, there is a strong trend towards an increase in patients with chronic renal failure who require dialysis therapy or kidney transplantation. A significant proportion are people over 60 years of age; according to various sources, patients in this age group account for 30% to 45 % of all patients requiring dialysis [1]. The annual increase in dialysis patients over 65 years of age is 2.5%, and the increase in the number of elderly patients on the waiting list reached 16.7% for 5 years.

The probability of receiving a kidney graft for the elderly is significantly lower than for young recipients, and the risk of complications and death in the dialysis treatment and transplantation is significantly higher, which complicates the therapy of this category of patients and makes it relevant to develop ways to increase the availability of kidney transplantation for elderly patients [2].

One solution is to use kidney grafts of suboptimal quality from suboptimal donors, including those over 60 years of age, as well as from younger donors in case of hypertension disease, stroke death, traumatic brain injury, if a donor with type 2 diabetes mellitus and impaired kidney function with increased blood creatinine levels above 1.5 mg/dL [3, 4]. Cardiac arrest donors ("asystolic donors") can be classified as both expanded criteria donors and optimal donors. The use of these donors has been noted to be able to increase the availability of kidney grafts for elderly recipients by 14% [5].

The advanced age of a recipient introduces a certain risk of developing a graft dysfunction due to the presence of concomitant diseases, which can worsen the immediate and long-term results of transplantation; and when a kidney is transplanted from an expanded criteria donor, the potential risk increases even more [6, 7]. Nevertheless, this approach is recognized by many authors as acceptable, since it provides a higher survival rate for patients after kidney transplantation and improves the quality of life compared to elderly patients treated with hemodialysis [8]. Analysis of all kidney transplant cases registered in Danish Nephrology Registry Scandiatransplant from 1995 to 2011 showed that when transplanting a kidney from a cadaveric donor, the risk of death in elderly recipients is reduced by 55% compared with continuing treatment of these patients with hemodialysis, and for those with Charlson Comorbidity Index scored 5 or higher, the risk of death is reduced by 72%. The overall survival of these recipients was 62% after transplantation from a cadaveric donor, and 70% after that from a living donor.

Among the factors that potentially affect the kidney transplantation results in the older age group recipients, there is the presence of multiple comorbidities that limit the possibilities of transplantation [9, 10]. Their progression often leads to the death of a recipient with a normally functioning kidney graft [10–12].

The purpose of the study was to assess the effectiveness of kidney transplantation from suboptimal donors to patients of the older age group with signs of end-stage chronic renal disease.

Material and methods

The study was based on analyzing the medical records of 124 patients who underwent cadaveric kidney allotransplantation at the

N.V. Sklifosovsky Research Institute for Emergency Medicine in the period from 01.02.2016 to 01.03.2020. Of these, 69 (55.6%) recipients were over 60 years old (Group 1). These patients were among 116 patients of the older age group included in the waiting list for kidney allotransplantation under the program for improving the efficiency of care for elderly patients with end-stage renal disease (ESRD). During the follow-up period, the analysis also included 55 patients under 60 years old (44.4%), who made up the comparison group (Group 2).

The mean age of all recipients was 64.3±2.2 years old. Distribution of patients by age was as follows: 55 patients (44.4%) at the age of 55-60 years, 37 patients (29.8%) at the age of 61-65 years old, 27 patients (21.8%) aged 66-70 years, 5 patients (4.0%) were over 70 years old. The ratio of men and women was 45 men (65.2%) and 24 women (34.8%) in the 1st group, and 29 men (52.7%) and 26 women (47. 3%) in the 2nd group. So, men predominated in both groups, and to a greater extent in the 1st group; however, the difference between the groups in this parameter were not statistically significant.

The main causes of the ESRD development were diabetic nephropathy (24 patients), polycystic disease (27 patients), chronic glomerulonephritis (38 patients), and urolithiasis (21 patients). Significantly rarer causes of ESRD were primary chronic pyelonephritis (3 patients), renal amyloidosis (3 patients), gouty nephropathy (3 patients), systemic vasculitis with kidney involvement (2 patients), lupus nephritis (1 patient), and nephropathy of unknown origin (2 patients). All examined patients had a number of concomitant diseases: cardiovascular diseases had been diagnosed in 49 patients (71.0%) of the first group, and in 18 (32.7%) patients of the second, chronic lung diseases were present in 26 patients (37.7%) of the first group and in 7 (12.7%) in the second group, infravesicular obstruction was documented in 31 patients (44.9%)

of the first group and in 5 (9.0%) in the second group; degenerative diseases of the musculoskeletal system, chronic urinary infection and chronic cystitis also occurred in equal proportions in both groups. Recipients of the 1st group turned out to have a more severe somatic pathology with a more number of concomitant chronic diseases, isolated or in combination with other conditions, including those related to the organs of the genitourinary system. All patients underwent a standard examination in the preoperative and postoperative periods. We analyzed in dynamics (for up to 1 year) the recipient survival rate, the temporal characteristics of the kidney graft functioning, the case rates of immediate and delayed graft function development, rejection crises, parameters the graft functional status, the incidence and type of complications in the early and late postoperative periods. Based on these parameters, we assessed the feasibility of kidney transplantation in patients of the older age group, including those with a history of concomitant urological diseases.

Statistical analysis was performed using Microsoft Excel and Statistica 10.0 software packages. The normality of the distribution of digital values in the groups was assessed using the Kolmogorov test. Arithmetic mean values (M), mean frequency of features (P), and errors of mean values (m) were calculated.

Fisher's exact test was used to compare data from different groups with a normal distribution of data, and the Mann-Whitney test was used for an abnormal distribution. The presence and degree of correlations were determined using the Spearman correlation test. Depending on r value, the correlation degree was assessed as follows: the correlation was considered as pronounced at values from 1.0-0.7, moderate at values from 0.69-0.4, and weak less at values less than 0.39. Differences between

groups and the presence of correlations were considered statistically significant at $p<0.05$.

Results and discussion

Our analysis of the rates of using suboptimal donor kidneys for transplantation in the N.V. Sklifosovsky Research Institute for Emergency Medicine revealed an increase in such transplantations over the analyzed period. The share of such transplants changed from 17.9% (5 of 28 transplants) in 2016 to 54.5% (18 of 33 transplants) in 2017, 77.4% (24 of 31 transplants) in 2018, and up to 81.3% (26 of 32 transplant) in 2019 and for 3 months of 2020 (Fig. 1).

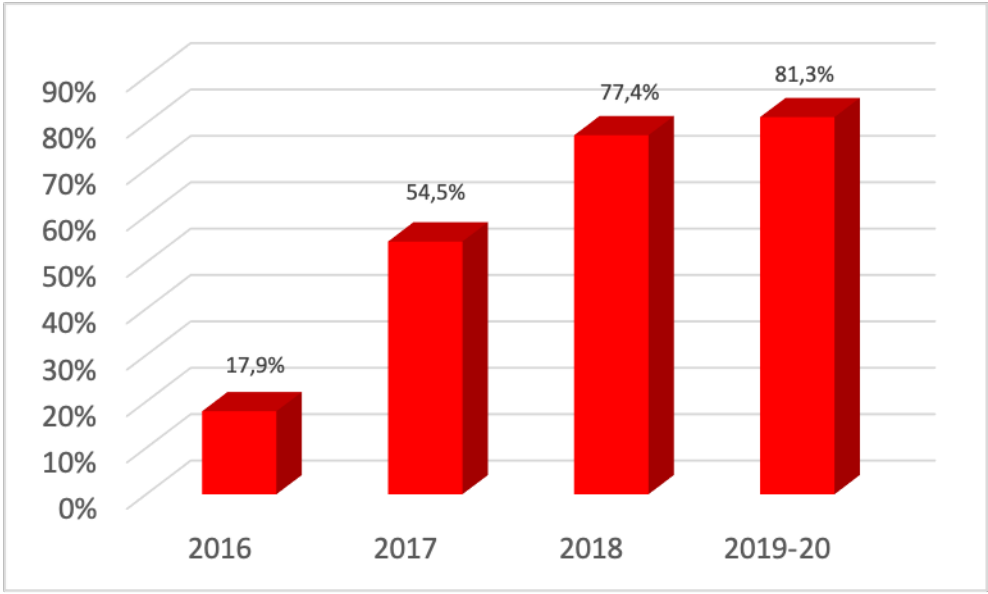

Fig. 1. Dynamics of the share of transplantations from suboptimal donors by years

To a greater extent, the rates of using suboptimal donor grafts increased in the patients group of the older age group. In general, 54 kidney transplantations from suboptimal donors (78.3%) and 15 transplantations from optimal donors (21.7%) were performed in the 1st group, while in the 2nd group, these figures were 19 (34.5%) and 55

(65.5%) transplantations, respectively. The difference in this parameter (the predominance of using suboptimal grafts in group 1) turned out to be statistically highly significant ($p<0.001$).

The ratio of kidney transplants from suboptimal and standard donors over the analyzed period increased from 7.1%/93.9% (2 of 28 operations) in 2016 to 42.4%/57.6% (14 of 33 operations) in 2017 year, up to 67.7%/32.3% (21 of 31 operations) in 2018, and up to 71.8%/28.2% (23 of 32 operations) in 2019-20 (Fig. 2).

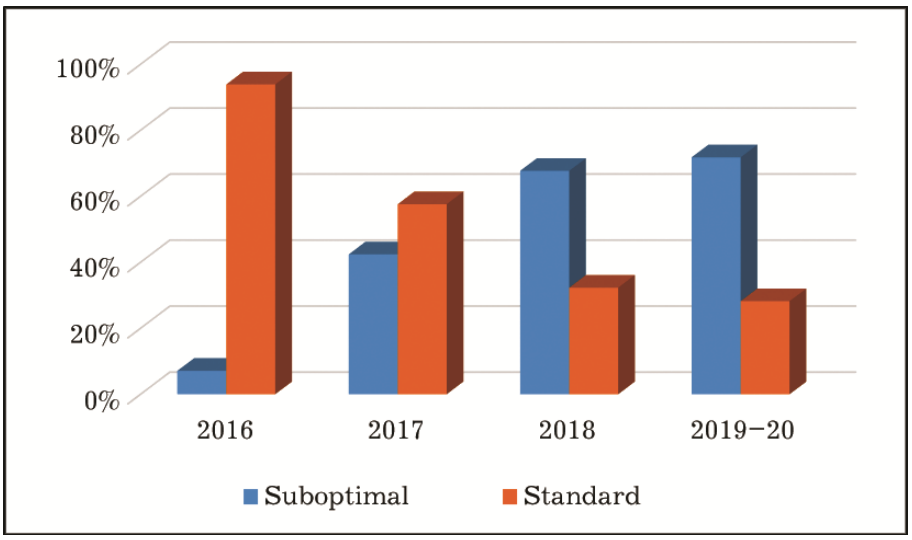

Fig. 2. The relationship in the share of transplantations from suboptimal and standard donors in percentage in different years of the study

The predominant use of suboptimal kidney transplantations in patients of the older age group can be explained by the implementation of the program aimed at increasing the access of elderly recipients for kidney transplantation in order to reduce the period of their stay on the waiting list.

In general, for the entire group of patients included in the analysis, the *recovery of the graft function* immediately after surgery was noted in

74.2% of cases (92 patients). Meantime, this figure made 63.8% (44 patients) in the 1st group, and 87.3% (48 patients) in the 2nd group. Accordingly, the delayed graft function of grafts was detected in general in 25.8% (32 patients), of which in 36.2% (in 25 patients) in the 1st group -, and in 12.7% (in 7 patients) in the 2nd group. Differences between groups were statistically significant at p=0.003. The relative risk of delayed graft function development in the patients of the older age group (RR) was 2.847 (95% CI 1.322-6.085).

Thus, in the recipients of the older age group, the delayed graft function of the transplanted kidney was significantly more often observed. This could be affected by 2 factors: the quality of grafts retrieved from expanded criteria donors, and the advanced age of recipients. We analyzed the impact of these factors.

Comparison of the rates of early graft dysfunction in recipients of this group showed that in cases of suboptimal donor kidney transplantation to patients of the 1st group, the incidence of delayed graft function was 52.4% (22 of 42 cases of suboptimal graft transplantation), while in kidney transplantation from optimal donor, the incidence of delayed function was 37.0% (10 of 27 cases of transplantation from a standard donor). Despite a 1.5-fold excess of the delayed graft function rates in kidney transplantation from a suboptimal donor, the differences were not statistically significant (p=0.213); however, the relative risk (RR) of developing this complication in recipients of a suboptimal graft was almost 1.5 times higher (RR=1.414, 95% CI 0.800-2.501).

Among the recipients of the 2nd group, in the case of kidney transplantation from a suboptimal donor, a delayed graft function was reported in 5 of 31 patients (16.1%), while in case of kidney transplantation from standard donors, this was observed only in 2 of 24 patients (8.3%). In this group, the statistical analysis of the means did not

reveal statistically significant differences (p=0.390), either, but the relative risk of significant kidney transplantation from a suboptimal donor was even higher: RR=1.935 (95% CI 0.419-9.127).

Both the recipient age, and the graft quality have an independent effect on the timing of kidney function recovery after kidney transplantation, since although no significant differences between groups differing by the recipient age and the graft quality have been found, the risk of developing a delayed graft function of the transplanted organ was higher with kidney transplantation from a suboptimal donor.

Incidence of graft rejection crises

Since the development of an acute rejection in the early postoperative period, as well as a delayed graft function, can play an important role in the recovery of the transplanted kidney function, we analyzed the incidence of this complication separately in the study groups.

Despite the pronounced differences, the statistical analysis using the χ^2 test and Fisher's exact two-tailed test did not reveal their statistical significance (χ^2=0.138, t=0.240, p>0.05).

In kidney transplantation to elderly recipients, there was a tendency to a rarer development of rejection crises and its milder course than in kidney transplantation to younger patients. The lack of statistical significance of the revealed differences is apparently explained by the relatively small number of cases in the study groups.

Despite a higher incidence of the delayed graft function in older age group recipients, the dynamics of the graft function recovery after a period of acute tubular necrosis in both groups was similar (with the exception of the cases with a primary graft non-function).

A comparative analysis showed that the mean time of graft function normalizing was 18.3±2.2 days in the 1st group, and 16.4±3.2 days in the 2nd group. In total, 33 hemodialysis sessions were performed in group 1, which made 0.44 sessions per patient; in group 2, 36 hemodialysis sessions were performed, which made 0.47 sessions per patient. Differences in these parameters between groups were not statistically significant (p >0.1).

When assessing the impact of the graft suboptimality and compromised medical history on the graft functional recovery after transplantation in the recipients of group 1, no statistically significant impact of these factors were identified (Table 1).

Table. The impact of donor suboptimality on recovery of the transplanted kidney function

Parameter	Standard graft	Suboptimal graft	Compromised medical history	p
Duration of graft dysfunction (days)	17.3±2.8	19.5±3.1	19.2±2.9	>0.05
Number of hemodialysis sessions per 1 patient	0.42	0.45	0.45	>0.05
Oligoanuria on day 7 (% of patients)	10.7%	12.4%	11.2%	>0.05
Polyuria (% of patients) after 15 days after 30 days	 26.6% 45.8%	 30.3% 51.8%	 28.9% 52.3%	 >0.05 >0.05
Creatinine level at discharge from hospital (μmol/L)	148±12	155±14	151±14	>0.05
Blood urea level at discharge from hospital (mmol/L)	11.2±0.6	12.6±0.7	12.1±0.5	>0.05

The results obtained indicate that, although the risk of a delayed graft function and irreversible ischemic damage increases when suboptimal grafts are transplanted to elderly recipients; nevertheless, the

functional recovery of transplanted kidney occurs in the same way as when transplanted to younger recipients and when transplanting a kidney from an optimal donor. A history of concomitant diseases does not significantly affect the dynamics of the graft function recovery.

Patient survival and the kidney graft functioning

Despite significant differences in the nature of the early graft function recovery (immediate or delayed) and the incidence of complications in the early and late postoperative periods in recipients of the older age group and younger recipients, this did not affect the patient survival. Within 1 year after allotransplantation, in each of the two groups, 1 patient died from disseminated cytomegalovirus infection. Thus, a 1-year recipient survival rate was 98.6% in the 1st group, and 98.2% in the 2nd group.

Meantime, significant differences were revealed between the groups in the duration of kidney graft functioning. In the early postoperative period (within 30 days after transplantation), 8 grafts were removed in group 1 due to a non-recovery of the graft function (primary graft non-function) (11.6%), while in group 2, only 1 graft was removed due to thrombosis of the vascular pedicle (1.8%). This difference was significant at $p=0.038$. In all 8 cases, the primarily non-functioning grafts were taken from suboptimal (expanded criteria) donors.

There were no cases of graft nephrectomy related to an uncontrollable rejection crisis in either of the two groups.

In the late postoperative period, 8 patients of the 1st group and 4 patients of the 2nd group underwent nephrectomy of the graft due to a continuously progressing graft chronic pyelonephritis and progressive loss of the graft function. One patient from group 1 developed an infection of the graft bed caused by the graft primary contamination with

Klebsiella pneumonia. Due to ineffective therapy and the development of bleeding from the lower epigastric artery stump with the involvement of the internal iliac artery in the inflammatory infiltration, the graft also had to be removed in this patient.

Thus, during the follow-up period (of 1 year), 17 grafts were lost in the 1st group (24.6%) and 5 grafts were lost in the 2nd group (9.1%) (significant difference at p=0.025).

The time changes in the proportion of grafts with preserved function in the groups during the follow-up period is shown in Fig. 3. At month 1 after transplantation, 88.4% and 98.2% of the grafts functioned in groups 1 and 2, respectively; after 3 and 6 months these figures did not change; after 9 months the figures decreased to 84.9% and 94.5%, respectively, and after 12 months they made 75.4% and 91.9%.

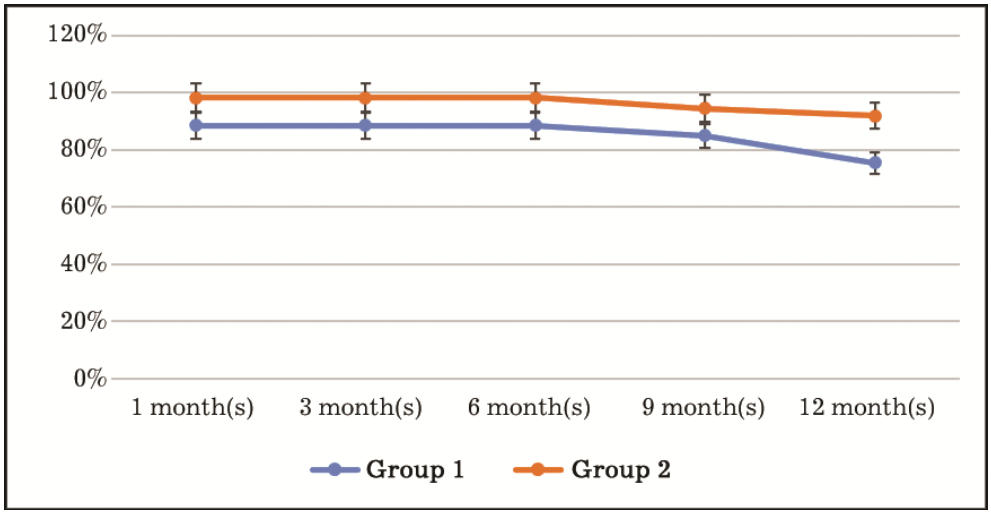

Fig. 3. The change in the rate of the maintained graft function cases over time

Status evaluation of the functioning grafts revealed their stable function during the follow-up period (up to 1 year) with a tendency in azotemia level to getting normalized. At month 3 months after transplantation, the blood creatinine level varied within 135-280 μmol/L

(mean 153±11 μmol/L), and after 12 months it ranged from 96-185 μmol/L (mean 126±8 μmol/L). For the follow-up period, the blood creatinine level was seen to get normalized in 25 recipients of group 1 (36.2%) and in 12 patients (23%) of group 2. The differences between the groups were not statistically significant (p=0.464).

Glomerular filtration rate after 3 and 12 months varied within 36-49 ml/min (mean 41±2 ml/min), and 38-55 ml/min (mean 43±2 ml/min), respectively, no statistically significant differences were identified in this parameter between the groups.

Thus, although the case rate of graft functioning within 1 year in recipients of the older age group was lower than that among younger recipients, nevertheless, transplantation was successful in 75% of these patients, which is a good indicator. At the same time, the graft loss did not result in fatal consequences; the survival rate of elderly recipients was 100%. Functional parameters of grafts in both groups were comparable.

Kidney transplantation in patients of the older age group is a topical issue, which has been recently investigated in a more and more number of studies. While the problem of kidney transplantation to elderly recipients has been widely discussed in the foreign press [6, 13–15], there are significantly fewer homeland publications on this issue [16, 17].

A comparative analysis of the kidney transplantation results in patients of the older age group and in the group of patients younger than 60 years showed that a 1-year recipient survival rates in the groups was nearly the same, amounting to 98.6% and 98.2%, respectively.

The survival rates for our recipients of the older age group in the immediate postoperative period are consistent with world statistics, according to which the age factor negatively affects the outcome in a longer follow-up period: mortality increases significantly at 5 and

especially 10 years after transplantation compared to that in younger recipients [18]. At the same time, a significant part of these recipients die from complications with a normally functioning graft. However, quite acceptable rates of early survival of elderly recipients inspire some optimism.

With regard to the timing of graft functioning, the analysis showed that in the group of elderly recipients, the early loss of a transplanted organ occurred statistically significantly more often than in younger patients ($p=0.025$). The main cause of this was the graft irreversible damage with the lack of the recovery of water and nitrogen excretion functions, which resulted in the organ removal in 11.6% of elderly recipients. In all those cases, the graft was obtained from a suboptimal donor.

Nevertheless, the graft functioning for 1 year in 75% of the older age group patients is close to the figures given by a number of foreign authors: 73.7%, according to A. Collini et al. (2009) [18], 76.2%, according to data from Collaborative Transplant Study (2014) [6], 82.1%, according to data obtained by J. Cabrera et al. (2020) [19], although some authors give even higher figures up to 92% [20].

Conclusion

The study results have shown that kidney transplantation from suboptimal donors to patients of the older age group provides acceptable results with low recipient mortality and a 1-year graft functioning rate of 75% of cases. This makes it possible to increase the availability of kidney transplantation for patients of the older age group and achieve better results in terms of their survival, provided to an adequate recipient selection and an objective assessment of the quality of transplanted organs is achieved.

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Information about the authors

Bidzina Z. Khubutiya, Physician of the Kidney and Pancreas Transplantation Department, N.V. Sklifosovsky Research Institute for Emergency Medicine, HubutiyaBZ@sklif.mos.ru

30%, collection and analysis of information and clinical material, writing the text of the manuscript, data systematization

Mogeli Sh. Khubutiya, Academician of the Russian Academy of Sciences, Prof., Dr. Sci. (Med.), President of N.V. Sklifosovsky Research Institute for Emergency Medicine; Head of the Department of Transplantology and Artificial Organs, A.I. Yevdokimov Moscow State University of Medicine and Dentistry, https://orcid.org/0000-0002-0746-1884, KhubutiyaMS@sklif.mos.ru

25%, editing, making corrections

Anatoliy K. Evseev, Dr. Sci. (Chem.), Leading Researcher, Department of the General Intensive Care, N.V. Sklifosovsky Research Institute for Emergency Medicine, https://orcid.org/0000-0002-0832-3272, EvseevAK@sklif.mos.ru

20%, collection and analysis of clinical material, data systematization

Anna V. Babkina, Assoc. Prof., Cand. Sci. (Med.), Gynecologist of the Urgent Gynecology Department, N.V. Sklifosovsky Research Institute for Emergency Medicine, Associate Professor of the Department of Transplantology and Artificial Organs, A.I. Yevdokimov Moscow State University of Medicine and Dentistry, https://orcid.org/0000-0002-5342-8268, BabkinaAV@sklif.mos.ru

25%, collection and analysis of clinical material, data systematization.

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